Zespół Omenna u kuzynów: różny przebieg kliniczny i identyczna mutacja genu RAG1.

Omenn's syndrome in cousins: different clinical course and identical RAG1 mutation

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STRESZCZENIE

Zespół Omenna jest rzadką postacią ciężkiego skojarzonego niedoboru odporności związaną z wysoką śmiertelnością. W pracy zaprezentowano różnice w przebiegu klinicznym i wynikach badań laboratoryjnych u dwóch kuzynów z tym zespołem i z identyczną mutacją w genie RAG1.

Słowa kluczowe: zespół Omenna, mutacja genu RAG1

SUMMARY

Omenn's syndrome is a rare inherited form of severe combined immunodeficiency associated with high mortality. This report presents the clinical course and laboratory findings in two cousins with Omenn`s syndrome which were different despite of the identical mutations in RAG1 gene.

Key words: Omenns' syndrome, RAG1 mutation

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Introduction

Omenn's syndrome (OS) was described for the first time in 1965 by Gilbert Omenn in a child of consanguineous parents [1]. It is a rare autosomal recessive disease belongs to group of severe combined immunodeficiency (SCID) characterized by symptoms of erythrodermia, eosinophilia, hyper IgE, lymphadenopathy and hepatosplenomegaly. The majority of children with OS may be classified as $T^+B^-NK^+$ SCID. T cell counts are normal or elevated with oligoclonal T cell receptor repertoire with Th2 phenotype, and B cells are mostly absent. White blood cells counts (WBC) are frequently increased, due to eosinophilia and/or lymphocytosis. The level of immunoglobulin (IgG, IgA, IgM) is normal or decreased but the level of IgE is very high. In majority of patients with OS the genetic defect, missense mutations of the recombination activating genes 1 and 2 (RAG1/2) what lead to partial V(D)J recombination activity is noted [2–5]. The identical mutations of these genes are observed in clinical syndrome presenting the expansion of oligoclonal Tγδ cells, autoimmune cytopenias and disseminated cytomegalovirus (CMV) infection [6]. However, null mutations in RAG1/2 genes are associated with SCID characterized by absence of mature T and B cells (T-B-SCID) [3]. Moreover, the clinical and immunologic features of OS were described in patients with and ARTEMIS or IL7RA mutations [7]. The differential diagnosis of OS includes the Omenn-like syndrome caused by engraftment of maternal T cells [4, 8].

This report presents two patients from the same extended family, with classical clinical and immunological features of OS due to the similar homozygous mutation in the RAG1 gene. The clinical symptoms and course of disease of these two patients were different including the presence of unusual feature of OS e.g. deep neutropenia (agranulocytosis) in one patient. In this child, molecular analysis of T-cell receptor (TCR) genes showed oligoclonal patterns.

Patient 1.

The boy weighting 3 200-g was delivered spontaneously at 38-week of gestation to a gravida 4 para 4 mother with Apgar score of 10 at 1st minute. He was vaccinated with BCG and engerix B without complications. The previous family story included the death of two girls (born in the distance of 2 years) both due to sepsis; first at age of 2 months and the second at age of 2 days. The skin lesions diagnosed as *ichtyosis congenital* were associated with high number of eosinophils and susceptibility to infection. The 3rd child (boy) is healthy. The patient was admitted to the hospital at the age of 25 days with initial diagnosis of *ichtyosis congenita*, in good clinical condition.

Physical examination revealed erythrodermia, hepatosplenomegaly and lymphadenopathy. Apart from erythematous rash and exfoliation of the whole body skin, the enlargement of bilateral cervical, axillary and inguinal lymph nodes was noted. The liver was palpable 3 cm and the spleen 2 cm beneath costal arch. WBC count was 28 000 cells/mm^3 (6% neutrophils, 35% eosinophils, 56% lymphocytes, 3% monocytes) (table 1). Liver and renal function tests were normal. Tests for CMV infection were positive. *Staphylococcus cohnii MRCNS*, MLS was cultured in

the blood. Immunological tests revealed normal levels of serum immunoglobulins: IgG, IgA, IgM and very high level of IgE. Flow cytometric analysis showed increased percentage and absolute number of T cells, normal proportion between $CD4^+$ and $CD8^+$ T lymphocytes. The vast majority of T cells were $CD45RO^+$. B lymphocytes were absent (table 2, 3). Percentage and absolute number of NK cells were within the normal range. The response of lymphocytes to stimulation of mitogens in proliferation test was slightly decreased. Omenn's -like syndrome was excluded due to negative results of mother T lymphocytes chimerism test. Based on clinical features, results of laboratory tests and the family story, the diagnosis of Omenn's syndrome was considered. To confirm the diagnosis of OS genetic tests were performed. Direct fluorescent sequencing of the *RAG1* gene showed a homozygous deletion of two nucleotides. No mutations were detected in the *RAG2* gene.

Shortly after admission of the patient bilateral pneumonia was diagnosed and treated with amikacin, cefuroxime supported with oxygen therapy. Co-trimoxazole, ganciclovir sodium, ketoconazole and methylprednisolone hemisuccinate were added according to diagnosis of OS and CMV infection. Moreover, the cytomegalovirus specific antibodies (cytotect) was used once as supportive therapy of CMV and substitution with intravenous immunoglobulins (IVIG) was introduced every three in standard dose (500 mg/kg body weight). Blood culture became negative and clinical condition improved. After pneumonia therapy the prevention of bacterial infections with ceftazidime and than amoxicillin was provided for prolonged time. He was bottle-fed but despite high protein diet (2,7 g/kg/24 hours) the protein levels were still low (50,5 g/l). During hospitalization the patient developed chronic diarrhea caused by *Rotavirus*. As a routine for SCID children therapy, Hick-

Table 1. Numbers of white blood cells (WBC) at first examination in patients with Omenn syndrome

Patient	No 1		No 2		Age-matched normal values	
White blood cells (cells/μl x 10^3)	28,0		19,6		5,0-20,0	
Lymphocytes	% of WBC	cells/μl x 10^3	% of WBC	cells/μl x 10^3	% of WBC	cells/μl x 10^3
	56	15,68	8	1,568	56	2,5–16,5
Neutrophils	6	1,68	26	5,096	40	1,0–9,5
Eosinophils	35	9,8	62	12,152	3,5	0,07–1,00

Table 2. Humoral and cellular immunity parameters at first examination in patients with Omenn syndrome

Patient	No 1		No 2		Age-matched normal values	
Serum immunoglobulins (g/l)						
IgG	5,67		9,59		3,83–10,10	
IgA	<0,06		0,08		0,02–0,14	
IgM	0,34		0,73		0,13–0,64	
IgE total (kU/ml)	38 000		37 500		0,00–60,00	
Lymphocyte subpopulations	% of lymph	cells/μl	% of lymph	cells/μl	% of lymph	cells/μl
CD3	90	9000	70	1190	53–84	2500–5500
CD4	38	3800	58	986	35–64	1600–4000
CD8	46	4600	11	187	12–28	560–1700
CD19	1	4	2	78	6–32	300–2000
HLA-DR	76	6840	56	1638	5–8	135–232
TCR$\alpha\beta$	89	8900	62	1054	89–97	2225–5335
TCR$\gamma\delta$	2	200	8	136	1–9	25–495
Natural killer cells	3	300	12	204	4–18	170–1100
Lymphocyte proliferation (cpm)					Control group*:	
Medium	768		616		1367±1110	
PHA	7722		2026		51899±2969	
Anty-CD3	8477		655		48785±24025	
PWM	8660		2033		50255±21594	

* Control group – healthy 34 children (18 girls and 16 boys), the medium age 2,1±1,1 years

mann catheter was inserted in the left jugular internal vein. Irradiated red blood cells were transfused four times because of progressive anemia. The therapy with steroids resulted in improvement of skin and decrease of eosinophils but deep neutropenia (447 neutrophils/µl of total WBC 14 900/µl) was still noted, so the subcutaneous injections with recombinant human granulocyte-macrophage colony-stimulationg factor (GM-CSF) in a dosage of 250 µg/m^2 body surface were introduced. This therapy was ineffective (no increase of neutrophils number) and was terminated after 11 days. There was no bone marrow examination because of a short episode of cardiac arrest during biopsy procedure with effective reanimation procedures. The clinical symptoms of infection occurred again and *Staphylococcus haemoliticus* was isolated from the blood. The antibiotics (cefepime dihydrochloride and linezolid) were used according the pathogen sensitivity assay leading to clinical improvement and negative blood culture tests. The unexplained episode of marked increase in total WBC count (84 600/µl) with the neutrophils percentage below 5 and enlargement of lymph nodes was noted but increased dose (up to 2 mg/kg/24 hrs) of Methylprednisolone hemisuccinate for one week lead to decrease of WBC (20 000/µl). The dose of steroids was reduced and the side effects slowly resolved. The HLA-matched unrelated bone marrow donor and the child was transferred to the Bone Marrow Transplantation Center for further therapy.

Patient 2

This boy was born at 39-week of gestation, weighing 3,5 kg at birth. He was delivered spontaneously to a gravida 3 para 3 mother with Apgar score of 10 at 1-st minute. His father and mother of previous patient's are siblings (fig. 1). In this family the previous 2 children (boy and girl) are healthy. He was vaccinated with BCG and engerix B without complications. The clinical symptoms and family story (the previous patient was hospitalized in the same regional hospital) suggested Omenn's syndrome and the boy was sent to Immunology Ward at the age of 1 month. The physical examination revealed erythrodermia, hepatomegaly, lymphadenopathy without splenomegaly. Apart from erythematous rash on whole body skin, the patient had also papular squamous eruption on the face and scalp, exfoliation of the skin in the nape and ankle region. In the anal region – oozing erosions were found. Cervical, axillary and inguinal lymph nodes were enlarged. At admission WBC count was 19 600 cells/µl (26% neutrophils, 62% eozynophils, 8% lymphocytes, 4% monocytes) (table 1). Liver and renal function tests were normal. Blood, urine, stool and skin cultures were negative for bacterial infection. Tests for CMV (excretion in urine, blood PCR) were

Table 3. Results of flow cytometric analysis of lymphocytes B and T at second examination in patients with Omenn syndrome

Patient	No 1	No 2
B lymphocytes (% within lymphogate)		
CD19$^+$	0,08	3,6
Igκ/Igλ ratio	0,5	1,8
T lymphocytes (% within lymphogate)		
CD3$^+$	98,2	75,3
CD4$^+$	29,1	63,7
CD8$^+$	67,9	9,1
CD4/CD8 ratio	0,4	7
HLA-DR$^+$	20,4	6,1
CD3$^+$T-cells (% within lymphocyte T gate)		
CD4$^-$/CD8$^-$	1,6	6,8
CD45RO$^+$	99,8	98,6
CD45RA$^+$	3,1	7,2
TCRαβ$^+$	98,8	94,8
TCRγδ$^+$	1,0	5,2
CD127$^+$	65,2	91,8
β_2 microglobulin	present	present

Table 4. *TCRB* and *TCRG* PCR heteroduplex and GeneScan analyses

Patient	No 1	No 2
TCRB genes primer combinaton	PCR product:	PCR product:
Vβ2/Vβ24-JβA (FAM) multiplex	clonal	oligoconal
Vβ2/β24-JβB (FAM) multiplex	clonal	oligoconal
Dβ1/Dβ2-Jβ (FAM) multiplex	clonal	oligoconal
TCRG genes primer combinations		
Vγlf/Vγ10-Jγ1121/Jγ1323 (FAM) multiplex	clonal	oligoconal
Vγ9/Vγ11-Jγ1121/Jγ1323 (FAM) multiplex	clonal	oligoconal

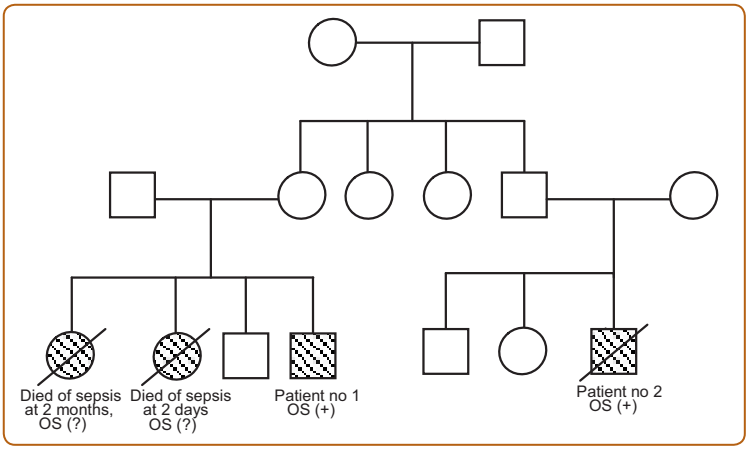

Fig. 1. Pedigree of patients with Omenn's syndrome (OS). The mutations of RAG1 gene were determined only in patients 1 and 2. squares = males, circles = females, slash = deceased, shaded = affected, not shaded = healthy

negative. Tentative diagnosis of Omenn syndrome was confirmed by the results of immunological and genetic tests. The percentage and absolute number of B cells were low and the percentage and number of T cells and NK cells were within the normal range. The majority of T cells expressed CD45RO (table 2, 3). Direct fluorescent sequencing of the *RAG1* gene showed a homozygous deletion of two nucleotides in the *RAG1* gene. No mutations of the *RAG2* gene were detected. Similar to patient 1, Omenn-like syndrome was excluded based on negative results of chimerism test with mother's T lymphocytes.

The child was bottle-fed. On admission he received intravenous cefuroxime, amikacin therapy as a continous therapy because ofr *Staphylococcus aureus* bacteriemia observed in regional hospital. As a routine for SCID patients; co-trimoxazole, ketoconazole, ganciclovir sodium, methylprednisolone hemisuccinate (0,4 mg/kg) and IVIG substitution (every three weeks in dose 500 mg/kg) were included into therapy schedule. After the procedure of catheterization of Hickmann catheter into left jugular internal vein patient needed intubation and positive pressure ventilation with supplemental oxygen because of diffused inflammatory changes in both lungs. Blood cultures were negative. The modification of therapy included total parenteral nutrition, antibiotics (including cefepime dihydrochloride) and irradiated red blood cells because of progressive anemia. Ganciclovir sodium and IVIG were continued. During a bronchial toilet patient demonstrated two episodes of short cardiac arrest (a few seconds) following with tetraplegia and loss of pain sensation, bulbar signs. Cranial ultrasounds did not reveal any abnormalities. Therapy was continued and in next few days the patient condition gradually improved so the diagnosis of brain edema was established. Physical examination showed alleviation of neurological symptoms and enteral feeding was slowly introduced. After extubation the oxygen support was required because of the circulatory-breathing unsteadiness. The following episode of high temperature, increase of WBC (8 000 cells/µl with 61% neutrophils, 1% eosinophils, 30% lymphocytes and 5% monocytes) and blood culture showing *Staphylococcus haemoliticus MRCNS* and *Enterococcus foecalis* was noted. The therapy with linezolid and vancomycin adjusted to pathogen sensitivity was withdrawn because of allergic reaction. Moreover, the therapy with amikacin, piperacyllin and meropenem were ineffective and septic fever with blood cultures was noted. The patient respiratory function deteriorated again. He developed pulmonary edema and required endotracheal intubation with positive pressure ventilation. The blood cultures and clinical symptoms (regularity of fever) suggested local catheter infection. Following this the catheter was removed with significant improvement of clinical status and negative results if blood cultures. The new central venous catheter was inserted and HLA-typing of the patient and his family performed. The compatible unrelated donor was found and the child was transferred to Bone Marrow Transplantation Center. Despite of severe clinical course the patient was in stabile status, without symptoms of infection but with tendency to cardio-vascular instability and respiratory problems.

Molecular studies

Clonality diagnostic.
PCR heteroduplex and/or GeneScan analysis of the *TCRB* and *TCRG* genes of patient 1 showed monoclonal PCR products (table 4). These results suggested the presence of monoclonal T cell population.

In patient 2 PCR heteroduplex and/or GeneScan analysis of the *TCRB* and *TCRG* genes showed oligoclonal PCR products what made unlikely the existence of monoclonal T cell population, taking into account the detection limit of 5–10%. However, these results might indicate (antigen driven?) selective outgrowth of T cells, in line the diagnosis Omenn syndrome.

Direct fluorescent sequencing

Direct fluorescent sequencing of RAG1 gene of both patients showed a homozygous deletion of two A nucleotides at position 368 and 369 (numbering according to NCBI M29474). This deletion in a frame shift lead to an altered amino acid position 86 onwards and a premature stop codon at position 118. Direct fluorescent sequencing of the RAG2 gene showed no mutation (NCBI M94633).

Discussion

It is known that OS is rather rare form of SCID (about 1:50 000 live births) whereas the most often SCID (T-B+) is diagnosed in about 1:200 000 live births. However, during the last few years, on the Immunology Ward of Polish-American Institute of Pediatrics, OS was the most often observed SCID from Małopolska region (2–3 cases per year). Mother of patient 1 and father of patient 2 were sibilings. Both of them and their sponses derived from the same small village in Małopolska. Moreover in the family history there is common ancestor in the distant past (a founder effect?).

Clinical features of OS are: erythrodermia, lymphadenopathy, hepatosplenomegaly and eosinophilia. The mutation of recombinase genes RAG-1 and RAG-2 impair variable diversity joining (VDJ) rearrangements, what are required for the maturation of T and B lymphocytes. In half of OS patients this mutations

are missense type [5]. This mutation leads to development of poorly functional T lymphocytes and lack of B lymphocytes. The antigens stimulation resulted in expansion of Th2 subpopulation of T lymphocytes but with the expression of restricted TCR VDJ set (oligoclonal population). Absence of B mature lymphocytes is seen in lymph nodes as lack of germinal centers. The modified development of T lymphocytes is associated with underdevelopment of thymus including low number of Hassal's corpuscles and depletion of T lymphocytes. Moreover, a profound reduction in the level of mRNA for some proteins (e.g. fatty acid-binding protein, cyt p450/a2) was found in thymus of OS patients` [9]. There are observations that few residual T cell clones may escape negative selection in thymus and thereafter expanded in periphery. The functional repertoire of these T cells might cause massive autoimmune reactions [9, 10].

The clinical symptoms of patients with OS represent two groups: – common and similar in all patients (e.g. erythrodermia, lymphadenopathy, hepatosplenomegaly) and different between individual patients. In majority of cases [11, 12] the level of IgE is very high because of stimulation by IL-5 overproduced by Th2 lymphocytes. The similar mechanism based on overproduction of IL-4 is associated with eosinophilia seen in almost all patients with Omenn's syndrome. In minority this mechanism is no so strong and the eosinophilia is mild and level of IgE within normal range [13, 14]. In our patients eosinophilia and extremely high level of IgE was noted in both of them. Moreover, patient 1 demonstrated the maturation of myeloid cells narrowed to eosinophils line and absence of neutrophils in consequence. This agranulocytosis was resistant to steroids and growth factor (neupogen) therapy. Unfortunately, more detailed assay of bone marrow hematopoiesis was impossible because of patient's reaction to biopsy procedure.

The lymphocytosis is common in patients with OS although normal value of lymphocytes is noted in part of patients [15]. The both possibilities were noted in our patients as patient 1 demonstrated hyperleukocytosis with hyperlymphocytosis, whereas patient 2 charaterized normal value of leukocyte and lymphocyte counts. Leukocytosis of patient 2 was below 20 000/µl even during bacterial septic episodes and steroids therapy what suggested limited possibilities of production by bone marrow. In patients 1 the infection was associated with increase of leukocytosis (lymphocytosis) up to 80000/µl with agranulocytosis. These lymphocytes were sensitive to steroids and higher dose was enough to obtain decrease the number but still above normal value. All T cells were of autologous origin, as a lack of chimerism excluded maternal engrafment. Increased numbers of circulating $CD45RO^+$, $HLA\text{-}DR^+$ T lymphocytes was observed. Characteristic feature of OS is the massive expansion of oligoclonal T lymphocytes. We found oligoclonal TCR repertoire in patient no 2, however, monoclonal T cell population was present in patient no 1. The function of lymphocytes of both patients was abnormal what is consistent with other data [16]. The different clinical features observed in our patients suggested differences in regulating mechanisms despite of similar genetic defect and consanguinity between our patients.

The level of IgG was within normal level but below 5 months of age it is presumably maternal origin. However, serum IgM levels were also within normal ranges. Hypogammaglobulinemia is generally found in older infants suffering from OS, thereby suggesting transplacental acquisition of immunoglobulins in the younger ones.

In both of our patients the vascular symptoms were significant what was probably associated and might explain the episodes of edema (including cerebral), leakage syndrome (mainly into lungs during septic bacteriemia observed in patient 2) and cardiac arrest noted in patient 1 during bone marrow biopsy. There is no data about such clinical symptoms in OS and the mechanisms are unknown. The high level of IgE is usually believed as associated with allergic reaction what might explain allergy to antibiotics observed in our patients 2 with OS including skin rush despite of prolonged therapy with steroids. However, in available literature no case of OS demonstrated such symptoms.

Genetic analysis of the RAG1 and RAG2 genes confirmed the clinical diagnosis as both boys had the same missense mutations in both alleles of RAG1 gene. However, there were some differences in clinical course of their disease. The most striking feature of patient 1 was neutropenia/agranulocytosis resistant to therapy, which is not a common phenomenon in OS patients. However, the case of RAG1 mutation and severe neutropenia was presented [17]. In this case predominance of $\gamma\delta$ T cells, autoimmune blood cell manifestation and severe viral infections were noted what suggested a new variant of SCID [6, 17]. The immunophenotype of T lymphocytes from peripheral blood of our patient 1 showed expression of TCR α/β exclusively what suggested different, unknown mechanisms of bone marrow failure in this patient. Phenotypic presentation of RAG1 gene mutation may show the variety of symptoms depending not only upon the location and type of mutation but also probably on other genetic factors and environmental influences.

The different clinical course of OS presented by our patients suggested different, patient-tailored therapy despite of general, routine indication of therapy in SCID patients. Despite of clinical symptoms the main indication for therapy is bone marrow transplantation (BMT) what suggested the priority of HLA antigens

typing and vascular catheterization in SCID patients. The stabilization of patients' status, clearing of infections and improvement of skin changes are crucial for BMT but the time of hospitalization before BMT in such patients is very important for their condition and success of BMT.

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